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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,931	09/22/2003	Poh K. Hui	N0469.70022US02	1625

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
11/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,931	HUI ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 9-11-08 is acknowledged.

Claims included in the prosecution are 87-117.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 87-111 and 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) or Unger (6,521,211) by themselves or in combination in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Nyberg et al. disclose methods of preparing phospholipids precipitates comprising mixing a phospholipids blend containing phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin in an organic solvent mixture of polar organic solvent (e.g. methanol) and essential non-polar organic solvent (e.g. toluene), concentrating the solution, then add a second organic solvent of intermediate polarity (e.g. acetone and heptane) to cause precipitation of phospholipids at about 13°-25° C, and drying the precipitate (see example 1, 2, 6, and claim 1). The concentration of sphingomyelins in the solvent is 2-20 mg/ml (column 6, lines 44-48). Nyberg et al. specifically indicate separation of phospholipids into different phases (column 5, lines 53-57; example 1, lines 56-67; and example 2).

Unger et al. teach a process for preparing phospholipids comprising DPPA, DPPE- PEG5000, and DPPC (column 135, lines 29-31). The phospholipid mixture is added to a non- aqueous solvent system of methanol and toluene (column 135, line 34). The mixture was warmed to 55°C and allowed to form a thick gel (column 135, lines 36 and 39). Methyl t-butyl ether was added to the mixture to precipitate the solid material at 25°C and placed in a vacuum oven to dry (column 135, lines 40-42 and 44).

Nyberg et al and Unger teach steps a, b and c. What is lacking in Nyberg and Unger is the teaching of the preparation of lipid suspensions or liposomes using the lipids of Nyberg et al and Unger (steps d and e).

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent

taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

It would have been obvious to one of ordinary skill in the art, if lipid encapsulation of an active agent is desired, to use the steps taught by Kissel or Papahadjopoulos or Lenk to prepare liposomes since it is an art known method of preparing liposomes. Although the references do not teach all of the non-aqueous solvents such as propylene glycol and their amounts, since the principle of precipitation is the same and since Nyberg teaches the use of suitable solvent systems (col. 3, lines 6-1 and col. 9, lines 54-57), in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to use any solvent which is suitable with a reasonable expectation of success. Similarly, since the purpose is to dissolve the lipids in a solvent, it would have been obvious to one of ordinary skill in the art to use suitable temperatures to achieve the complete dissolution of the phospholipids. Applicant's claim limitation of sterilizing filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

3. Claims 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) or Unger (6,521,211) by themselves or in combination in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Nyberg, Unger, Kissel, Papahadjopoulos and Lenk have been discussed above. These references do not teach how to prepare liposomes containing ultrasound contrast agents containing perfluoropropane, that is, exchange air with perfluorohydrocarbons in a vacuum chamber.

Swaerd-Nordmo while disclosing vesicular preparations containing contrast agents teaches that the contrast agents can be incorporated by the exchanging perfluoropropane in a vacuum chamber (col. 3, Example 1). Various phospholipids which could be used are taught on col. 3, line 60 through col. 4, line 28).

It would have been obvious to one of ordinary skill in the art to use the method of Swaerd-Nordmo to encapsulate perfluoropropane in the teachings of the primary references if the intended purpose is to use the liposomes for the delivery of ultrasound contrast agents since such a method is known in the art as taught by Swaerd-Nordmo.

4. Claim 115 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) or Unger (6,521,211) by themselves or in combination in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Swaerd-Nordmo (6,165,442).

The teachings of Nyberg, Unger, Kissel, Papahadjopoulos, Lenk, Kikuchi and Swaerd-Nordmo have been discussed above. What is lacking in these references is the final sterilization of the product. Such a sterilization however, would have been obvious to one of ordinary skill in the art if the preparation is used for human administration especially by an injection mode since sterilization of contrast agent containing

liposomes by gamma-ray irradiation is known in the art as taught by Unger 6,071,495) (see

5. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg ((5,677,472) in view of Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination, further in view of Unger 6,416,740.

The teachings of Nyberg, Kissel, Papahadjopoulos and Lenk have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

6. Claims 87-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination.

Kissel teaches a method of preparation of liposomes (lipid suspension). The method involves dissolving the phospholipid (lecithin) in methylene chloride and adding an aqueous solution of a biologically active agent, IL-2 (Example B1 on col. 13). The lipids taught include phosphatidylcholines and sphingomyelin (col. 3, lines 1-51).

Similarly Papahadjopoulos teaches a method of preparation of liposomes wherein the phospholipids are dissolved in diethyl ether and adding an aqueous solution

of the active agent (example 4 and claims). Various phospholipids could be used (columns 4 and 5).

Lenk similarly teaches a method of preparation of liposomes wherein the phospholipids are dissolved in an organic solvent and adding an aqueous medium (examples and claims). The lipids used include sphingomyelin (col. 7).

Kikuchi teaches a method of preparation of liposomes wherein heated propylene glycol containing lecithin or DPPC is added with an aqueous solution. Other solvent taught is polyethylene glycol. Kikuchi further teaches sizing the liposomes using polycarbonate filters (col. 3, lines 33-46; examples and claims).

In essence, these references teach steps d and e of claim 87. Instant steps a-c in claim 87 just recite re-precipitation of the lipids used in the formation of lipid suspension. The criticality of these steps is unclear to the examiner if one is using pure phospholipids just as used in Kissel, Papahadjopoulos, Lenk and Kikuchi. Since the removal of impurities by precipitation is well-known in the art of chemistry, instant claims are deemed obvious to one of ordinary skill in the art. The reference of Nyberg which teaches selective precipitation of sphingomyelins is already of record. Applicant's claim limitation of sterilizing filter in claim 107 is noted. However, Kikuchi teaches the filtration of the liposomes using filters and this process results in sterilization. The examiner cites in this context, the reference of Papahadjopoulos (6,210,707) which teaches liposomal suspensions are sterilized when filtered through a conventional filter (see col. 17, lines 35-44).

7. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kissel (4,863,740) or Papahadjopoulos (4,235,871) or Lenk (4,522,803) or Kikuchi (4,687,661) individually or in combination as set forth above, further in view of Unger 6,416,740.

The teachings of Kissel, Papahadjopoulos, Lenk and Kikuchi have been discussed above. What is lacking in these references is the use of claimed lipid combination (DPPA, DPPE- PEG5000, and DPPC) in the preparation of the liposomes.

Such a use however, would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Unger shows that this lipid combination is routinely used for the preparation of lipospheres (examples 3 and 12).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK